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REVIEW

The neurobiology of interoception in health and disease

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Interoception is the sensing of internal bodily sensations. *Interoception* is an umbrella term that encompasses (1) the afferent (body-to-brain) signaling through distinct neural and humoral (including immune and endocrine) channels; (2) the neural encoding, representation, and integration of this information concerning internal bodily state; (3) the influence of such information on other perceptions, cognitions, and behaviors; (4) and the psychological expression of these representations as consciously accessible physical sensations and feelings. Interoceptive mechanisms ensure physiological health through the cerebral coordination of homeostatic reflexes and allostatic responses that include motivational behaviors and associated affective and emotional feelings. Furthermore, the conscious, unitary sense of self in time and space may be grounded in the primacy and lifelong continuity of interoception. Body-to-brain interactions influence physical and mental well-being. Consequently, we show that systematic investigation of how individual differences, and within-individual changes, in interoceptive processing can contribute to the mechanistic understanding of physical and psychological disorders. We present a neurobiological overview of interoception and describe how interoceptive impairments at different levels relate to specific physical and mental health conditions, including sickness behaviors and fatigue, depression, eating disorders, autism, and anxiety. We frame these findings in an interoceptive predictive processing framework and highlight potential new avenues for treatments.

Keywords: interoception; health; mental health; predictive processing; autism; anxiety; depression; eating disorders

Introduction

A fundamental responsibility of the brain is to keep itself, with the rest of the body, alive. The brain coordinates the regulation of vital inner processes, including blood pressure, digestion, and breathing, by flexibly reacting to external and internal changes. Interoception refers to the sensing of the internal state of the body,[1] providing the afferent channel of the interplay between body and brain that allows homeostasis (i.e., maintenance of physiological stability) through covert reflexes (e.g., baroreflex), motivational drivers (e.g., hunger and thirst), and explicit bodily sensations (e.g., breathlessness, bladder distension, or gastric pain). Interoception is differentiated by this inward bodily focus from exteroceptive senses (e.g., vision and audition)[2] that process information about the outer world, and more proximate senses (e.g., proprioception, touch, and taste) that use the body to describe the external environment and its relation to it. Interoceptive information is communicated through a set of distinct neural and humoral (i.e., blood-borne) pathways with different modes of signaling, which the brain represents, integrates, and prioritizes. How these central representations of the inner body are generated and interact is an important focus of interoception research, not least because of the implications for a range of cognitive and behavioral processes and disorders. A comprehensive understanding of cognition, emotion, and overall well-being must incorporate an understanding of interoception. The same questions are consequently integral to the field of health neuroscience.[3] Interoceptive processing has a key role in health and disease, and research is systematically delineating the ways in which brain–body relations can alter a person's well-being.

Interoception involves a relatively restricted set of classes and channels of information (e.g.,

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cardiovascular, gastric, and respiratory).These differ with respect to the generation of the signal (organ stretching, mechanoreceptive, and chemoreception) and their afferent pathway (neural and humoral).[4] Complexity within interoceptive signaling arises more from the need to parse and integrate information originating from multiple organs and across wide temporal domains than from the need to differentiate, uniquely characterize, and encode complex novel stimuli (even in the generalization of immunological responses). Nevertheless, continuous, dynamic, and diverse information about internal bodily function is integrated within shared neural substrates supporting distributed interoceptive representations and associated experiences (feeling states). Together, these shape the generative (autonomic or hormonal) control of bodily states and steer adaptive behaviors (e.g., a drop in blood sugar levels leads to foraging).

One theoretical framework to frame the dynamics and dimensions of interoception is *predictive processing* (PP).[5–7] PP is a hitherto mainly hypothetical model (with growing evidence) of neural function that assumes a functional and cortical hierarchy, where models about incoming signals are generated, compared with, and lastly improved by, actual sensory input. Originally developed as a principle for exteroception (e.g., vision), PP was recently applied to interoception (interoceptive predictive processing; IPP).[2,8,9] IPP describes the hierarchical processing schemes that may underlie brain–body interaction. For IPP, where informational parameters are arguably more restricted, yet under more direct neural control, the cerebral cortex might dominate only at higher order representational levels.

In this article, we review the dimensional nature of interoception, approaches to their quantification, discuss the neurobiological basis of interoception, and how these findings can be framed within IPP. We offer our perspective on the implications for both physical and mental health, and scrutinize the contributing role of interoception to different health conditions. Finally, we suggest how interoception research can further enhance health neuroscience.

Dimensions of interoception

Interoception is defined by both its origin within, and reference to, the inner state of the body. This single term generalizes communication through multiple distinct physical axes, and representations that unfold at different anatomical and psychological levels, on different timescales. Interoception is a concept that implicitly suggests the integration of different types of sensory information. However, inconsistency within the physiological and psychological literature regarding the definition of interoception, and use of terms such as *interoceptive awareness*, led to proposed dimensional frameworks for understanding and studying this set of senses.[10,11] Within such a framework, interoception can be described from the physical responses in body and brain representation up to (and beyond) interoceptive metacognitive (i.e., available for explicit awareness and reflection) insight and conscious awareness.

The first dimension of interoception refers to the afferent, interoceptive signal that is communicated to the brain from one or more internal organs, which can be measured, for example, by evoked changes in central neural activity, for example, as a change in neuroimaging signal or heartbeat evoked potential (HEP).[12] HEPs refer to a change in neural activity (measured using magnetoencephalography, electroencephalography, or intracranial neural recordings) that occurs after a heartbeat. Interestingly, HEP amplitude typically correlates with the ability of an individual to detect and report their heartbeats.[13]

The second dimension reflects the impact of visceral afferent signals on other forms of central sensory or cognitive processing and behaviors. This level does not necessitate (or preclude) perceptual awareness (i.e., consciousness) of the interoceptive signal or other processes. Illustrations of this interoceptive dimension are found, for example, in cardiac timing experiments where afferent heartbeat signals affect decisions, emotional processing, and memory.[14–16]

Three "psychological" dimensions refer more directly to the perception of interoceptive signals: interoceptive accuracy, sensibility, and awareness.[10] These dimensions developed from the use of tests of interoceptive sensitivity/ability, such as heartbeat-detection tasks.[a] These tasks are designed to rate

[a]Classic methods to assess interoceptive accuracy include heartbeat tracking[17] and heartbeat-discrimination

individual differences in the ability to sense internal bodily signals, which might account for variation in emotional temperament or psychosomatic vulnerability.[33] Typically, an interoceptive task requires a participant, at rest (i.e., usually sitting or lying down in a laboratory setting), to report "felt" interoceptive sensations (e.g., the timing of a heartbeat): Interoceptive accuracy refers to objective performance on such behavioral tests, for example, how accurately they perform a heartbeat-tracking task.[17] Next, interoceptive sensibility describes subjective belief about one's own ability to consciously perceive bodily signals, ascertained via self-report measures, such as questionnaires (e.g., body perception questionnaire; BPQ),[34] or reflected in their rated confidence in their performance accuracy on an interoceptive task. Since subjective and objective rating can diverge, a level of conscious insight can be calculated: Metacognitive interoceptive awareness expresses this insight into interoceptive performance aptitude and is derived from confidence–accuracy correspondence.[10] This metacognitive dimension of interoception is a most appropriate use of the word "awareness" in the context of interoception.

A further "executive" dimension on this interoceptive dimensional framework attempts to capture the degree to which an individual is able to flexibly attend to, and utilize, interoceptive information or can adaptively switch between interoceptive and exteroceptive representations.[11] The conscious perception of bodily sensations is an important yet broad topic. Most theoretical approaches to interoception and consciousness focus on the role of bodily processes for phenomenal selfhood,[8,35–37] where interoceptive events provide a bodily anchor for experiences of selfhood.[38] A more pressing question, however, is which circumstances elicit conscious awareness of internal signals, such as the sudden awareness of heartbeats in fear-related scenarios. The subjective impression of body perception and actual accuracy in perceiving interoceptive signals can diverge,[10] raising the issue of how and when precise bodily signals are consciously represented.

The neurobiology of interoception

Convergent evidence identifies the insular cortex (IC) (Fig. 1) as the brain substrate underpinning higher order interoceptive representations: for example, the left posterior IC is reliably engaged when attention is directed to one's heartbeat, relative to an exteroceptive focus.[39] Also, anterior IC (AIC) activity predicts objective performance accuracy on interoceptive tasks. In particular, right AIC functional reactivity predicts interoceptive accuracy on a heartbeat discrimination task and its volume predicts interoceptive sensibility.[1] The IC is buried between the adjacent frontal and temporal lobes. The architecture of insula changes (including progressive loss of the granule cell layer) from the posterior to AIC, with other subregional differences in cellular organization. The ICs are bidirectionally connected to the cingulate, prefrontal, parietal, and medial temporal cortices and subcortically to basal ganglia:[40] The AIC is strongly connected with the anterior cingulate

tasks.[18–20] Indeed, these two tasks are widely and principally used to indicate accuracy, although empirical assessments often use only one of the methods as a sole proxy for interoceptive ability, with the majority of the current work dependent on the heartbeat-tracking task.[21–24] The two cardiac interoceptive tasks tap into different processes,[25] with the tracking task based on the sensing of internal physiological information, but also potentially amenable to higher order influences such as knowledge about heartrate;[26] and the discrimination task requiring coupling information proceeding from exteroceptive and interoceptive channels.[10,27] Both tasks share similar and distinct functional architecture.[28] Beliefs about heartrate have been shown to influence performance on the tracking task, leading some researchers to question its validity.[29] Moreover, performance on these two cardiac tasks can diverge,[30] and the relationship between heartbeat perception and other bodily axes of interoception, such as respiration and gut, is scarce and inconsistent.[25,31,32] Therefore, the generalizability of findings derived from the heartbeat-tracking task is questionable. From an IPP perspective, sensory evidence or predictions related to certain modalities may be weighted more heavily than that of other modalities. Conditions in which cardiovascular sensations may be of less relevance than sensations from other modalities (e.g., eating disorders) suggest that this may be indeed the case. Thus, the assumption that the heartbeat-tracking task can serve as a valid proxy and the potential differential weighing of interoceptive sources needs to be treated with caution. Further research using additional interoceptive tests, covering a wide range of visceral signals, is needed to comprehensively understand the role of interoception in health and disease.

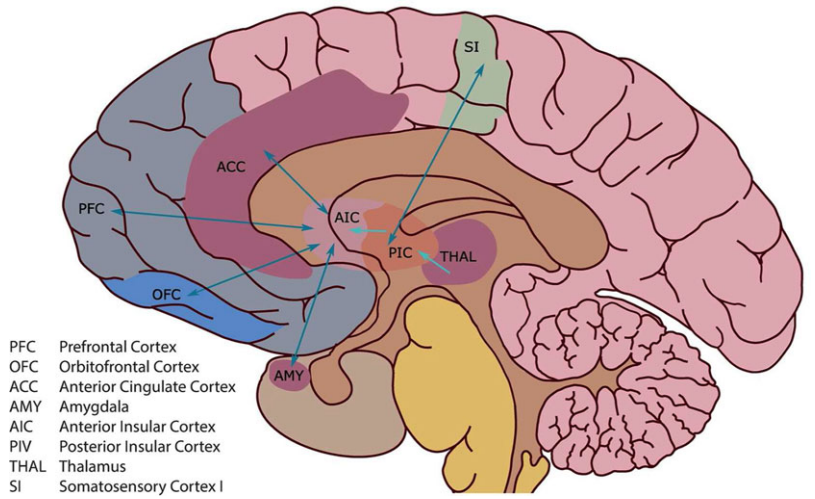

Figure 1. **Diagram of insula connectivity. The insular cortex divides into the posterior (PIC) and anterior (AIC) insula. The PIC receives afferent input from the thalamus (THAL) and is reciprocally connected with the primary somatosensory cortex (SI). Within the insula, the PIC projects interoceptive information to the AIC. The AIC strongly connects bidirectionally with the anterior cingulate cortex (ACC), amygdala (AMY), prefrontal cortex (PFC), and the orbitofrontal cortex (OFC), forming a functional network.**

cortex (ACC), arguably forming a functional unit with the amygdala and ventromedial/orbitofrontal cortex (VMPFC/OFC), to which they are mutually linked. The posterior insula (PI) has stronger reciprocal connections to the second somatosensory cortex, and receives direct afferent input from the interoceptive thalamus (posterior ventromedial nucleus, which has a lighter corollary projection to the ACC), relaying interoceptive and nociceptive information. Interoceptive information is projected within the PI (i.e., primary viscerosensory cortex implicated in primary, objective representations of bodily signals), and rostrally to the AIC, which serves to rerepresent and integrate interoceptive signals with exteroceptive and motivational information.[41]

The higher order representation of interoceptive information within the AIC and its projection regions underpin consciously accessible feelings that inform emotions and motivate behaviors. This representation also shapes the operational functioning of the brain, as it continuously receives and responds to such homeostatic afferent signals. An important aspect of this higher order representation is the integration across distinct categories of signals that possess distinct temporal response characteristics and encode hormonal, metabolic, thermal, immunological, nociceptive, and viscero-motor information. This information reaches the brain through humoral and neural pathways.[42] Microglial transduction pathways additionally inform about, and even engage the brain in, inflammatory status, where inflammatory mediators lead to waves in microglial activation that is propagated across the brain.[43] However, the loss of anatomical specificity, temporal structure, and perceptual distinctiveness may be obligatory characteristics of a dynamic higher order integrative interoceptive representation, from which may emerge an amorphous affective feeling state that is the predictive platform for motivational behavior, emotional experience, and internal homeostatic control. Hypothetical models of brain function state that higher order representations require nonspecificity to enable abstract and future-directed predictions to ensure flexible adaptation to potentially disruptive events.[2]

Nevertheless, well before the IC, conscious access, and affective feeling states, afferent viscerosensory information is processed within subcortical and brain stem regions supporting homeostasis (Fig. 2). The nucleus of the solitary tract (NTS) is the main region where visceral neural (spinal laminar 1 and vagus nerve) inputs converge within the brain stem[44] and is of critical importance for the control of physiological state (e.g., blood pressure

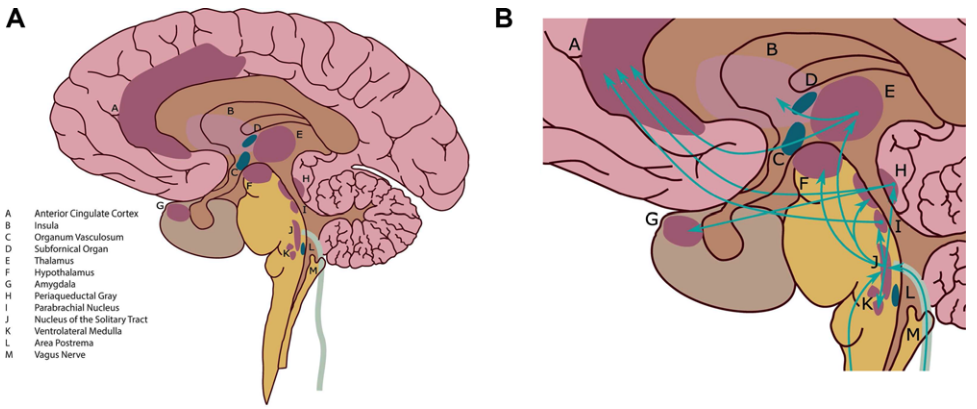

Figure 2. Schematic depiction of interoceptive brain centers and pathways in the human brain. Schematically depicted are interoceptive brain centers (A) and viscerosensory pathways (B) in the human brain. The circumventricular organs area postrema (L), organum vasculosum (C), and subfornical organ (D) provide access to the brain for chemicals circulating in the blood stream. Visceral afferents (blue arrows) enter the spinal cord (lamina 1) and spinothalamic tract, with outputs in the nucleus of the solitary tract (NTS; J), parabrachial nucleus (I), and periaqueductal gray (H), terminating in the thalamus (E). Viscerosensory inputs (green arrows) ascend mainly from the vagus nerve (M) and terminate in the nucleus of the solitary tract (J). The NTS projects to the ventrolateral medulla (K), parabrachial nucleus (I), periaqueductal gray (H), and the thalamus (E), from where inputs (green and orange arrows) are relayed to the hypothalamus (F), amygdala (G), insula (B), and the anterior cingulate cortex (A).

control). The NTS consists of a series of purely sensory nuclei and is organized viscerotopically, where neurons that receive input from distinct organs and types of visceral receptor are in close proximity. This specific organization hints to early integration of viscerosensory signals across related modalities.[45] The NTS projects to the hypothalamus, ventrolateral medulla, and parabrachial nucleus, and through these regions provides a first level of control of hormonal, immune, and autonomic outputs.[46] Chemicals circulating in the blood stream access the brain via specialist circumventricular organs (the area postrema, organum vasculoscum of laminae terminae, and subfornical organ). The humoral information is projected to the hypothalamus and NTS, contributing the negative feedback control and cross-modal homeostatic responses mediated through pituitary hormones and the autonomic nervous system.

The NTS receives from spinal visceral afferent neurons with cell bodies in the dorsal root ganglion containing motivational information from cranial nerves, notably the vagus nerve. Viscerosensory inputs with cell bodies in vagus nerve ganglia terminate in the NTS and project onto the pontine parabrachial nucleus and periaqueductal gray before an obligatory relay within the posterior ventromedial thalamus. These prethalamic midbrain pathways project further to the hypothalamus and amygdala, and complement the main viscerosensory thalamocortical projection to the IC (and the ACC).[47] Nevertheless, all levels of the neuroaxis representing interoceptive information are implicated in the autonomic control of internal physiological state and processes that shape emotions, feelings, behavior, and cognition.[8,35,41,42,47–49] Ultimately, the interplay of body and brain depends on bi-directional signal messaging, where higher level brain regions might influence bodily processes in a top-down manner, and afferent signals influence brain processes from the bottom-up. This complex and dynamic interaction is theoretically captured by an increasingly prominent framework, PP, or, more specifically, IPP.

Interoceptive predictive processing

General predictive processing

PP[5,6] is an algorithmic theory about neural function and cortical organization.[b] The rationale is that the brain only has an approximate access to external

[b]Although PP is praised as a very promising theory[6] that aims to provide a unifying framework for cognition, action, and perception,[5,7] critics voice concerns[50] about key assumptions of the theory being untested[51] or even untestable.[52] Most empirical demonstrations of PP

(e.g., environmental and bodily) states, requiring it to infer the most probable hidden cause of the multitude of sensory signals it receives. In order to steer the organism in an adaptive manner, a major goal of brain function is to filter out regularities on different spatial and temporal scales, and cancel out noise and irregularities.[7] PP suggests that the neural system achieves this by generating predictive models about the likelihood of incoming signals, whose probability is improved by feedback loops that are driven by the mismatch between signal and prediction (i.e., prediction error). Error signals serve to either update the model, perhaps generating a perception (i.e., perceptual inference), or by eliciting changes in behavior to improve world-model fit (i.e., active inference).[59] External signals thusly fundamentally alter predictive representations; causal regularities of brain–external matter are "folded into" predictions.[53] PP thereby allows for the influence of multiple factors, both from the top-down (e.g., environmental, social, cultural, and prior experience) and the bottom-up (e.g., genetic dispositions and hormone levels).

Although PP integrates these brain–external components into its theoretical horizon, it is mainly an account of neural function. The basic assumption is that predictive models are generated within cortical hierarchies whose representational array ranges from highly abstract regularities at higher levels to concrete sensory signal properties at lower levels. Timescales putatively differ from slow to fast as the degree of abstraction decreases.[60] Along this hierarchical organization, generative models travel downward, carrying predictions about the state of the level below, and are met by, and compared with, signals that are propagated back up to improve predictive power. The result is a dynamic and flexible cascade of top-down and bottom-up information canceling out prediction error. PP states that precision estimations of error signals (i.e., the probability of carrying valid signals with little noise) factor in this process. By reducing or increasing synaptic gain, prediction errors are weighed low or high. Only error signals that are deemed precise will be propagated back up and alter predictions.[6] According to PP, prediction error minimization is the brain's primary task in efficiently navigating behavior and experience.

Interoceptive inference

Interoceptive inference,[2,8] or IPP, takes up the general PP framework and applies it to internal body–brain interactions. Here, high-level predictions about the internal state of the body are generated within cortex (AIC is most strongly implicated) within a neural hierarchy, proximately involving the PI. Descending predictions are compared against incoming afferents, creating an error signal that serves to improve predictions and reduce subsequent prediction error through both perceptual inference (change in feeling state) and active inference (autonomic and behavioral response). It is assumed that these generative predictions cascade to earlier levels of control (including brain stem autonomic centers, which operate along similar negative control feedback principles), ultimately serving to keep bodily states within their expected range for adaptive behavior, thereby keeping the physiological integrity.

The Embodied Predictive Interoceptive Coding (EPIC) model[2] relates IPP and prediction error minimization more specifically to cortical architecture, offering a hypothetical model of IPP. By analogy to predictive coding within the motor system,[61–63] EPIC proposes that interoceptive predictions originate in the deep layers of the agranular (i.e., less laminar differentiation) visceromotor regions within the prefrontal (caudal VMPFC/OFC), anterior/mid cingulate cortices, and AIC. Back-projecting predictions are deemed to terminate within the superficial layers of dysgranular and granular cortical columns, where they alter an ongoing pattern of activity by changing the firing range of neurons in anticipation of viscerosensory input. These interoceptive inputs ascend from the NTS, parabrachial nucleus, via the thalamus to primary dysgranular and granular regions of the mid- and posterior IC.[64] Therefore, it is assumed that cortical prediction errors (i.e., difference between predicted and actual signal) are computed. The resulting prediction error signal is then projected onto the deep layers of the agranular visceromotor cortices, where the

in the brain remain indirect[53] and appear in the form of, for example, computational simulations[54,55] or repetition suppression effects.[56] However, new evidence keeps accumulating.[39,57,58] In this paper, PP is treated as a model of neural functioning, parts of which are rather speculative, or are inferred from existing evidence.

prediction originated.[c] At this point, the error signal can trigger the generation of new descending predictions that are ultimately expressed as the autonomic/visceromotor outputs. This process is interoceptive active inference minimizing future prediction error through generating interoceptive inputs that confirm predictions. Alternatively, the error may trigger a reduction of further signal sampling to reduce subsequent prediction error (affecting feeling state). Lastly, another option is that the error signal adjusts the precision of prediction units within the visceromotor cortices thereby modulating sensory sampling and viscerosensory input through adjusting the gain on the thalamo–cortical communication.

The EPIC model of IPP also suggests, in line with the general principle of PP, that interoceptive sensations are largely driven by predictions. This means that the perception of bodily signals is weighed toward mostly top-down, rather than bottom-up, cortical processes. The perception of bodily sensations is thus determined by predictions that are informed by prior experience and kept in check by actual bodily states. The extent to which these predictions lead to perception also depends on precision weighing across the interoceptive hierarchy, where precision units reflect both the reliability of predictions and prediction errors to increase or decrease the gain on error signals in order to change predictions. PP claims that precision instantiates attention, as estimates of reliability determine the impact of error signals on prediction units. Attention is thus thought to be the consequence of an increase in gain on prediction errors, rendering them apt to drive responses, behavior, and learning.[66] A well-functioning precision-weighing system is paramount for healthy functioning, as will become more obvious later in this paper.

EPIC assumes that interoceptive predictions interact with other sensory modalities, projecting onto visual, auditory, and somatosensory networks, to provide an embodied representational context for perception, cognition, and action. This way, interoceptive representations modulate responses across the brain, which serves as a reference for exteroceptive process and enables a dynamic multisensory representation of the body in its environment. Interoceptive predictions may thusly determine behavioral and perceptual patterns steered toward enabling and maintaining overall integrity. The agranular cortices, the putative origin of interoceptive predictions, are likely less constrained by incoming signals from the body.[2] This in turn may permit abstract and future-oriented predictions, enabling the system to flexibly adapt to and anticipate ever-changing demands (allostasis), instead of merely maintaining fixed set points in a reactive manner (homeostasis). IPP therefore encapsulates the flexible interplay between top-down and bottom-up processes that supports a stable, yet dynamic, internal environment.

In a healthy brain, predictions are informed by prior experience, situational context and state of the system, the comparison between prediction and actual incoming bodily signal, and precision estimation that results in a well-balanced interaction of brain and body. The goal of this complex process is to keep bodily states within a functional range that permits flexible adaptation to both internal changes and external challenges. The interoceptive system balances anticipated demands and deviations, efficiently regulating needs and resources. This process was conceptualized as "allostasis" or "predictive regulation"[67] and it underpins the well-being of body and mind.

Interoception in health and disease

The processing of interoceptive signals in the brain informs central control processes involved in maintaining physiological integrity. Interoception is tightly related to the predictive control of bodily signals that contribute to a system being able to maintain homeostatic set points, and a flexible allostatic regulation of more complex demands. When the system fails to respond to demands in an adaptive manner, or when predictive fluctuations fail to foresee necessary demands, the organism may reach allostatic overload and succumb to sickness and disease. Interoception research is increasingly demonstrating that the signaling and detection of internal bodily signals is important for physical and

[c] EPIC, IPP, and PP assume brain function to be implemented in a hierarchical manner. This hierarchy does not represent rigid step-by-step processing, but rather a highly context-sensitive, reconfigurable dynamical system whose patterns of effective connectivity change on a moment-to-moment basis depending on task, and internal and external contexts.[61,65]

mental well-being.[68] Interoceptive and emotional processes share underlying neural substrates,[11] and prominent theories of emotion even suggest that emotional feeling states arise through the sensing of bodily signals.[69–72] Emotional impairments accompany the majority of mental disorders,[37] acting as one potential route linking interoception to mental health.

Health and disease have distinct behavioral and experiential profiles that can be characterized by the presence or absence of reported symptoms and changes in behavior. PP claims that conscious perception is the product of prediction error minimization where the hypothesis with the highest posterior probability populates consciousness.[73] Probability distributions depend on prior experience (predictions), sensory effects (prediction errors), and the flexible weighing of their precision.[74] An important consequence is that perceptual content is determined by the estimated reliability of both prior knowledge and sensory input.[75] Under this assumption, prediction errors need to be precise or unsuppressed to determine conscious perception. Van den Bergh and colleagues[76] offer a plausible account of the role of interoceptive inference in the occurrence of reported symptoms. They suggest that interoceptive signals rarely reach awareness in the state of health, as interoceptive events are within the expected range (i.e., low prediction error). Interoceptive sensations are considered to arise only when signals are unexpected, thus eliciting prediction errors that are sufficiently precise to reach awareness. Interoceptive sensations are interpreted as symptoms when the hypothesis with the highest posterior probability contains information representing aberrant, disease-related, causes.[76]

Below, we review the role of interoception and interoceptive inference in several health conditions whose symptomatic profile shows that mental and physical health are often inextricable.

Sickness behaviors

The human immune system communicates immunological and inflammatory states to the brain via interoceptive pathways.[42] Peripheral states of infection and inflammation are transmitted to the brain via vagus nerve pathways, cytokines that circulate humorally, and via immune cells.[42] Responses to these insults include the activation of cardiovascular and gastrointestinal reflexes, the regulation of peripheral immune reactions,[77] and also a stereotyped pattern of responses called sickness behaviors (SBs).[78] These entail fatigue, reduced calorie and fluids intake, social isolation, anhedonia, and fever.[79] SBs potentially facilitate counteracting responses to infection and inflammation by inducing behavioral patterns that reduce bodily strain (e.g., fatigue motivates rest), and risk of additional infection (e.g., social isolation). This narrow repertoire of behaviors is evoked as a response to a wide range of infectious and inflammatory conditions, which suggests that they may form a coordinated general physiological and motivational reaction to a particular type of interoceptive challenge for the protection of the body's integrity.[80]

Experimentally, these mechanisms can be explored by administration of substances that cause a brief spike in inflammation, for example, typhoid vaccine,[81] infusion of endotoxin,[82] or inhalation of antigens.[83] A neurally mediated interoceptive pathway, recruiting the basal and posterior ventromedial thalamus, and dorsal mid- and PI, is activated after typhoid vaccination.[84] Specific components of SBs are associated with functional changes within interoceptive brain regions, including the mid-insula (fatigue),[84] subgenual cingulate (mood change),[81] and the midbrain substantia nigra (psychomotor slowing).[85] The insula is further implicated in the expression of inflammation-induced subjective experiences of fatigue, malaise, and social disconnect.[86] Increase in the right anterior insula (AI) metabolism tracks the loss of interest in social interaction,[87] while heightened connectivity between the AI and middle cingulate cortex predicts subjective malaise and discomfort after induction of inflammation.[88] These findings indicate a role for the insula in mediating the experiential side of SBs, a hypothesis that is in line with the theoretical proposal and emerging evidence implicating the IC in subjective experience of conscious motivational and emotional states arising from IPP.[35,70]

The same brain regions that support emotions and affective regulation are thus involved in SBs (and their origin in IPP), highlighting a connection between inflammation, SB, and mood disorders.[86] Changes in motivation are a hallmark of both SBs and major depressive disorder.[89] Low motivation to move can be adaptive in the context of physical illness, as it enables energy conservation while

prioritizing resources for fighting off inflammation and infection. In the case of prolonged or very severe inflammation, however, these motivational changes can mark the onset of a depressive episode.[86] Motivational changes ultimately influence processing of reward-stimuli;[18,19] correspondingly, response to reward outcomes is altered following inflammation. This is reflected on both the neural and behavioral level; reactivity within the ventral striatum, a center of (predictive) reward processing[90] is decreased, and both subjective and objective measures of anhedonia (the absence of reactivity to positive stimuli) are increased.[82] Distinct brain areas connected with interoceptive processing play a major role in the regulation of homeostatically relevant behavioral motivations.[47,91] To maintain the organism's integrity, information about aberrant bodily states is conveyed by interoceptive pathways, ultimately enabling behavior to balance out equilibrium through motivational changes resulting in the necessary action.[42] Social withdrawal is another symptom that SBs and depression share. Not participating in social interaction often leads to feelings of isolation and loneliness, and contributes to the maintenance of depressed mood.[92] Inflammation, through interoception, thus facilitates processes that underlie and enhance feelings of social isolation; induce feelings of social disconnect;[93] and impair the processing of social cues.[94]

Taken together, SBs illustrate how perturbation of internal bodily states affects neural representations, emotional states, and executive behaviors. These reactive patterned responses are mediated via interoceptive pathways that typically support adaptive social, emotional, and motivational behaviors. The next section focusses on fatigue as an SB, chronic condition, and symptom of inflammatory or immunological diseases. Both SBs and fatigue can be conceptualized under the IPP principle, as will be detailed in the following.

Fatigue

Fatigue is a disorder that is characterized in the ICD-10 as a long-term condition that includes severe and constant feelings of tiredness, trouble concentrating and carrying out daily activities, generalized aches and pains, fever, and sleep disturbances.[95] It can be part of SBs, and as such have adaptive effects in that it prioritizes rest to save resources and may facilitate the role of fever in fighting off infections.[96] Fatigue can also appear on its own as a chronic condition (chronic fatigue syndrome),[97] which affects approximately 20% of the general population.[98] Its prevalence increases to 50%, however, as a symptom in conditions that are associated with a compromised immune system,[99] such as cancer,[100] autoimmune diseases like multiple sclerosis,[101] and fibromyalgia.[102] Fatigue is strongly associated with depression,[103] and listed in both DSM-5 and ICD-10 as a core criterion for major depression.[95,104]

Fatigue is a multidimensional construct that involves impairment of motor and cognitive processes, the subjective experience of fatigue, and behavioral changes affecting every day activities.[105] Research on fatigue emphasizes approaches that associate the condition with peripheral inflammation and its influence on brain structures involved in steering immunological responses.[79,106] Brain structures involved in fatigue include the insula and the frontostriatal network, most notably the ventral striatum.[107] In this context, signals of peripheral inflammation reach the frontostriatal network via immune-to-brain communication pathways that involve activation of microglia. This network underlies response to reward, which supports anticipation and motivation, both of which are reduced in fatigue.[108] An altered frontostriatal network due to inflammation is thus one strong candidate for the neurobiology of fatigue.[107] AIC has been associated with the experiential quality of emotions and feelings, and is thought to play a key role in the experience of fatigue.[108] After the experimental induction of inflammation via typhoid vaccine, fatigue was predicted by altered reactivity within the mid- and PI, and the ACC.[81] This suggests that interoceptive signaling of inflammatory states, and their impact on brain regions that are associated with processing interoceptive input, is an important factor in subjective experience of fatigue and vitality/agency.

Newly emerging views on fatigue are turning toward approaches that do not only consider the bottom-up effects leading to fatigue, but that also take into account possible top-down influences. From a Bayesian perspective, SBs in general, and fatigue in particular, may occur as a consequence of aberrant metacognitive beliefs about the brain's capacity to predictively control bodily states.[109] These aberrant beliefs could be the product of immunological and metabolic

disturbances that remain unresolved, or may result from the chronic exposure to environmental or social stress. Chronic stress manifests physiologically,[110] for example, as increased cortisol levels,[111] or as impaired hypothalamus–pituitary–adrenal (HPA) axis activation.[112] The resulting disturbances feed back into cerebral circuits, where increased cortisol levels disrupt *N*-methyl-D-aspartate receptor function,[14] which has been claimed to be involved in the generation and updating of belief representations.[113] This positive feedback loop may be the basis for the metacognitive belief that the system is unable to regulate bodily states, due to a chronically occurring discrepancy (i.e., prediction error) between predicted (i.e., belief based) and sensed internal states. Resorting to SBs and fatigue may thus be an adaptive response to a metacognitive evaluation of the system's dysfunctional regulatory capacities that are manifested in the failure to reduce interoceptive prediction error.[109]

Further research is needed to determine if distinct levels of interoceptive processing accuracy are compromised in individuals with high levels of fatigue, which would indicate another possible source of maladaptive regulation of bodily states.

Depression

Major depressive disorder is associated with affective symptoms such as low mood, and negative cognitions such as pervasive negative thoughts and intense feelings of hopelessness.[114] In addition, somatic symptoms, including aches and pains, disordered sleep, loss of appetite, and fatigue are just as frequent and occur universally across cultures.[115,116] Recognition that somatic alterations are an important factor for changes in emotion and cognition has grown over the past decade.[22,117] Depression is associated with autonomic dysfunction, manifesting as decreased baroreflex sensitivity,[112,113] reduced phasic skin conductance responses,[14,118] and reduced heart rate variability.[118] In addition to autonomic alterations, signs of heightened inflammation have been documented in depression.[39] In a subset of individuals with depression, cumulative meta-analyses demonstrate raised inflammatory markers, particularly IL-6 and C-reactive protein.[40] Disturbances in brain function are linked to increases in peripheral inflammatory markers, where, for example, reduced functional connectivity of corticostriatal reward circuitry is observed in depressed individuals with elevated C-reactive protein.[58]

Healthy controls demonstrate a correlation between interoceptive accuracy and intensity of experienced emotions, where better accuracy correlates with reports of more intense feelings,[33] raising the possibility of an impairment in interoceptive accuracy in depression where emotional "numbness" is often reported. However, the experiments detailing patterns of altered interoceptive accuracy associated with depression present a more complex relationship.[22] The ability to accurately perceive one's heartbeat is negatively correlated with depression symptoms in healthy controls, an effect only found to manifest when coupled with high anxiety.[117] In an experiment that contrasted interoceptive accuracy across three groups (healthy controls, community sample with moderate depression, and a more severely depressed clinical sample), only the moderately depressed sample had significantly impaired interoception.[22] Interestingly, and counter to predictions, the more depressed group displayed levels of interoceptive accuracy comparable to the control group,[117] though this effect may have been influenced, in part, by medication status.[22] Increasingly, nuanced investigation of interoceptive behavioral impairments linked to specific clusters of symptoms (e.g., differentiating negative effect from emotional numbness) may reveal clearer associations in depression.

Decreased heartbeat perception accuracy is accompanied by significantly reduced HEP amplitudes in depressed individuals.[62] The neurocircuitry underlying attention to visceral interoceptive sensations was assessed in unmedicated individuals with major depressive disorder (MDD) relative to controls. Activity in the dorsal mid-insula and a network of brain regions involved in emotion and visceral control were decreased in the MDD group. Moreover, resting state functional connectivity between the amygdala and the dorsal mid-insula cortex was increased in MDD and predictive of depression severity.[46] Together, these results suggest that the brain representation of interoceptive focus may be altered in MDD.

From a theoretical approach, IPP (including the EPIC model) provides a potential insight into depressive mechanisms, extending to the hypothesis that structural abnormalities and dysfunctional metabolism within the agranular visceromotor

cortices may be underlying causes of depressive states, particularly when associated with inflammation and SBs.[2] Visceromotor cortical dysfunction causes imbalance between demand and response through overpredicting metabolic energy demands.[119] This may engender overactivity of the HPA axis and thereby increasing levels of proinflammatory cytokines,[66] causing concomitant alterations in the immune and endocrine system.[120] This aberrant process will compromise dependent coupling of interoceptive predictions and inputs at the thalamocortical level, leading to a speculated increase in interoceptive prediction errors. Downregulation of these noisy error signals by precision units leaves them less able to influence and inform predictions. To further reduce prediction errors, the interoceptive network is left with two principal options: maintaining the dysfunctional predictions, or generating afferents that match these predictions. The latter may lead to noisier signals that fail to update predictive models. This insensitivity to prediction errors might mean that faulty predictions will maintain metabolic energy demand, until the endocrine and immune system have reached their limit. Depression, according to EPIC, ensues when the error signals can finally no longer be ignored and must be reduced, enlisting SBs to conserve energy.[2] The insensitivity to prediction errors in combination with ever-more demanding predictions is hypothesized to lead to a "locked-in" (attractor state) brain that maintains a vicious cycle of faulty predictions and noisy error signals.[121] Inefficient energy regulation may underlie negative affect, biasing the system more toward avoidance behaviors and social withdrawal.[110] A hypothetical IPP model of depression (and fatigue) thus connects aberrant allostatic processes to imbalanced affective processing, driving both somatic and experiential emotional symptoms of depression.

Autism spectrum conditions

Autism spectrum conditions (ASCs) are classified as neurodevelopmental conditions that are associated with stereotypical and restricted behavioral patterns, altered sensory reactivity, and social and emotional difficulties.[122]

Research is currently investigating the nature of interoceptive deficits associated with ASCs. Work in children is divergent, with one study suggesting that interoceptive accuracy is intact in autistic children and adolescents (aged 8–17),[123] while a subsequent study found that interoceptive accuracy, ascertained using heartbeat tracking, was markedly impaired in a comparable child and adolescent autistic sample.[52] Impaired interoceptive accuracy has also been shown in autistic adults, demonstrated using the heart beat tracking task, where significantly lower interoceptive accuracy scores were observed relative to a matched control group.[27] One study, however, demonstrates data to suggest that autism per se does not necessarily lead to interoceptive impairments, but instead alexithymia, which is highly comorbid with ASCs, is associated with reduced interoceptive accuracy.[124] Alexithymia is a subclinical condition characterized by a reduced capacity to detect and identify emotions in oneself and others,[125] and thus the emotion-processing deficits in autism, characterized by high alexithymia, may be the principal driver for interoceptive impairments in ASC. A recent study revealed that impaired interoceptive awareness, but not interoceptive sensitivity, is linked to autistic traits, alexithymia, and empathy.[126] Other studies in nonautistic populations have demonstrated a link between high alexithymia and impairments in interoceptive accuracy.[127] Together, these results suggest that interoceptive accuracy may be impaired in autistic individuals, and that this may be particularly coupled with emotion-processing deficits.

In contrast to behavioral performance on interoceptive tests, interoceptive sensibility, assessed via self-report questionnaires, is elevated in autistic adults, despite these same individuals demonstrating a relative impairment in interoceptive accuracy.[27] This is in line with research documenting that interoceptive aptitude ascertained using self-report does not necessarily predict actual performance measures.[10] Moreover, it suggests that these interoception dimensions may further diverge in clinical populations, with autistic individuals having an overinflated belief in their interoceptive aptitude relative to their performance accuracy. This enlarged discrepancy between objective and subjective interoceptive performance denotes potentially poor interoceptive sensory precision in ASCs and is in line with accounts of autism conceptualized as a condition with an imbalance of the precision ascribed to sensory evidence relative to prior beliefs.[128]

Altered insula reactivity has been observed in autistic individuals across a variety of distinct emotion-processing tasks, including response inhibition of emotional stimuli,[129] processing of bodily expressions,[130] and the processing of incongruent emotional information.[131] ASC is also associated with altered intrinsic functional connectivity of anterior and PI regions and specific brain regions involved in emotion and sensory processing.[132] Together, these results suggest that altered sensory precision marked by reduced interoceptive accuracy underscored by aberrant insula activity and functional connectivity may contribute to emotion-processing deficits observed in ASC and alexithymia more generally.

Anxiety disorders

Anxiety disorders include panic disorder, agoraphobia, social anxiety, generalized anxiety disorder, and specific phobias.[104] Investigations into interoceptive alterations in anxiety disorders are mixed, reflecting the diversity of anxiety conditions and also the range of methodological approaches.[133] Studies have reliably found that interoceptive sensibility (i.e., self-report measures of interoception) is elevated in individuals with a variety of anxiety-related conditions.[134,135] In accordance with this, interoceptive accuracy is also frequently elevated in individuals with anxiety, indexed by heightened performance on heartbeat perception tests in patients with anxiety and elevated occurrence of trait anxiety symptoms with heightened interoceptive accuracy in nonclinical cohorts.[22,136] However, a straightforward relationship between elevated interoception in anxiety is challenged by a number of studies that either do not show a relationship,[54,56] or reveal a reverse relationship, with higher levels of anxiety related to reduced interoceptive accuracy.[50] Recent work partly reconciles these divergent findings, by demonstrating that it is the relationship between subjective and objective measures of interoception, which predict anxiety symptomatology (in both an autistic population and healthy controls).[27] Specifically, individuals with an elevated interoceptive trait prediction error (ITPE), derived from a propensity to belief one is interoceptively proficient despite relatively poor interoceptive accuracy, had heightened trait anxiety scores.[27] ITPE refers to the specific discrepancy in interoceptive dimensions describing low accuracy paired with perceived high self-reported sensitivity to internal signals. Here, the self-report measure (such as the BPQ) is a belief about general interoceptive aptitude, potentially serving as a prior. In contrast, metacognitive interoceptive accuracy depends on the moment-to-moment divergence of interoceptive dimensions, such as confidence–accuracy correspondence. This interoceptive predictive error is potentially consistent with theoretical work that has posited that the pathogenesis of anxiety is related to noisy interoceptive input in combination with noisily amplified self-referential interoceptive predictive belief states.[137]

Eating disorders

Eating disorders (EDs) are characterized by atypical food intake (e.g., restriction in anorexia nervosa, or binging and purging in bulimia nervosa), and are often accompanied by a distorted body image.[138] Poor interoception has been linked to body image concerns,[57] and a number of empirical findings converge to suggest potential disturbances in the processing of interoceptive signals in individuals with EDs. Interoceptive self-report in this population has been primarily probed using the Eating Disorder Inventory (EDI),[139] which assesses the subjectively reported ability to discriminate sensations of hunger and satiety, and to respond to emotional states. Patients with EDs report impairments in these abilities,[140] which could reflect a generalized deficit in interoceptive processing. Empirical findings support this in part, with studies demonstrating impaired interoceptive accuracy in anorexia nervosa patients relative to matched controls using a heartbeat perception test.[76,141] Other studies, however, fail to show impaired interoceptive accuracy in anorexia nervosa,[75] and instead document enhanced reported detection of interoceptive sensations.

To date, only few studies have investigated whether interoception is compromised in bulimia nervosa, although it is suggested that interoceptive processing deficits drive the symptoms and associated behaviors in bulimia.[61] One study investigating interoceptive accuracy in women with a current diagnosis of bulimia nervosa observed no differences in heartbeat-tracking task performance when correcting for the presence of covarying comorbid alexithymia, depressive symptoms, and anxiety.[142] In contrast, women who had recovered

from bulimia nervosa (without a prior diagnosis of anorexia nervosa) demonstrated significantly reduced interoceptive accuracy compared with controls.[91]

Neural representation of bodily state is altered in EDs. During an interoceptive attention task (focusing on the heart, stomach, and bladder), the individuals with anorexia nervosa display significantly reduced activation in the AI during heartbeat perception, and significantly reduced activation in the dorsal mid-insula during stomach interoception, relative to a matched control group.[143] Individuals with anorexia nervosa display reductions in functional connectivity in the thalamo−insula subnetwork, thought to reflect changes in the propagation of sensations that convey homeostatic imbalances.[30] Bulimia nervosa is associated with increased gray matter volumes within the ventral AI,[29] and binge ED is associated with increased insula activity when viewing food images after an overnight fast.[25]

Interestingly, altered interoception is not only found in patients who are currently suffering from an ED. Impairments in interoceptive self-report, as measured by the EDI, predict vulnerability to the development of EDs, as revealed in longitudinal studies.[144–146] It is not yet known whether other dimensions of interoception, such as interoceptive accuracy or neural processing of bodily state, would also demonstrate premorbid alterations. Nevertheless, interoceptive measures, at least ascertained via self-report, may serve as a marker for ED vulnerability, facilitating potential early intervention.

The exact nature of interoceptive impairment in EDs remains unclear, as it varies across the type of ED, and studies often do not take into account comorbidities, such as anxiety, depression, and alexithymia, which are also associated with aberrant interoception.[125,147] Differences in methodology also potentially contribute to further ambiguity, with objective and subjective dimensions of interoception being used interchangeably, and the interoceptive axis (e.g., cardiac versus gastric) requiring further differentiation and systematic evaluation. Behavioral, neuroimaging, and psychophysiological studies nonetheless show that several dimensions of interoception are affected in different types of EDs. Further research with terminological and methodological consistency could help to create a more differentiated account of how interoception contributes to, and maybe even predict, the occurrence of EDs.

Conclusion

There is increasing evidence that the signaling, sensing, and detection of bodily states are implicated in physical and mental well-being.[45,148] Interoception research contributes an important dimension to the field of health neuroscience, by providing a powerful explanatory understanding into the dynamic interactions between body, brain, and mind that underlie pathophysiological disturbances across physical and mental disorders. Capitalizing on strengthening theoretical frameworks, including IPP, further research needs to extend systematic interoceptive investigation across different bodily axes, and include measures of interoception that cover neural signaling, objective behavioral performance, subjective experiences and beliefs, alongside metacognitive measures, to delineate comprehensively interoceptive predictors of specific symptoms. Where aberrant interoceptive processing appears related to symptoms, therapeutic efforts targeting interoception could prove to alleviate specific conditions. Interventions based upon biofeedback, for example, could improve interoceptive accuracy. More accurate access to internal signals, in turn, may be helpful to contextualize them within a nonthreatening setting, potentially decreasing anxiety symptoms.[149] Understanding the precise nature of interoceptive deficits has important clinical implications, as insight into interoceptive mechanisms may reveal new therapeutic targets to promote novel interventions.

Competing interests

The authors declare no competing interests.

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